

## Short communication

Frequency of five cardiovascular/hemostatic entities as primary manifestations of SARS-CoV-2 infection: Results of the UMC-19-S<sub>2</sub>

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## 1. Introduction

Infection by SARS-Cov-2 is mainly characterized by fever and respiratory symptoms, with dyspnea and lung infiltrates in more severe cases [1,2]. Many patients also present a pro-coagulant state, which is biochemically detected by increased D-dimer levels and is related to

complications and a worse prognosis [1,3]. In this context, isolated case reports and short case series have suggested an increased risk of patients with COVID-19 to develop clinically relevant cardiovascular and hemostatic disturbances [3–7]. Nonetheless, many of these reports refer to hospitalized patients, and as hospitalization itself usually increases complications in bedridden patients with multidrug treatment

or in very poor condition, it is unknown if such cardiovascular/hemostatic processes are related to the pathogenesis of SARS-CoV-2. Focus on patients with COVID-19 at emergency department (ED) arrival could help to answer this question.

## 2. Methods

The UMC-19 (Unusual Manifestations of Covid-19) is a retrospective, multicenter, case-control, multipurpose project based on review of medical reports of patients attended at Spanish EDs seeking 10 processes that could eventually be increased by SARS-CoV-2. Details of the whole project have been previously published<sup>6</sup>. Five of these unusual manifestations correspond to cardiovascular/hemostatic disturbances: acute coronary syndrome (ACS), deep venous thrombosis (DVT), pulmonary embolism (PE), stroke and upper gastrointestinal bleeding (UGB). Study 2 (UMC-19-S<sub>2</sub>) was designed to analyze the frequency of these five cardiovascular/hemostatic manifestations in COVID patients attending EDs (cases) and compare these frequencies with those observed in the overall ED population (non-COVID patients, controls). Cases were all patients diagnosed with COVID-19 (either, microbiologically or clinically) between March 1st and April 30th, 2020 in the participating EDs (during this 61-day period, 213,435 cases of COVID-19 were confirmed in Spain). Controls were all non-COVID patients coming to EDs in a 2-month period (COVID period) and all patients consulting the ED between March 1st and April 30th, 2019 (pre-COVID period). Cardiovascular/hemostatic manifestations in cases and controls were first identified through the electronic system according to specific codes and were then manually reviewed in medical reports and confirmed by the principal investigator of each center. ACS included both myocardial infarction with or without ST elevation, and stroke included both ischemic and hemorrhagic events. The complete methodology has been extensively detailed elsewhere [8,9].

The relative frequency of the 5 above mentioned cardiovascular/hemostatic entities in ED comers in cases and controls was compared following two different strategies: 1) by comparing the relative frequency in COVID patients using non-COVID patients as comparator (altogether and also using the subgroups of non-COVID patients included in 2019 and 2020 separately); and 2) by comparing the relative frequency in 2020 with respect to 2019. In order to describe the main baseline patient characteristics, we collected age, sex and comorbidities for all cases presenting any of the 5 entities, and compared them with a sample of controls recruited by randomly selecting one control (1: 1) with the same diagnosis from the entire list of controls. Comparisons were performed using the chi square or ANOVA test, as needed.

## 3. Results

The case group included 63,822 COVID patients diagnosed in 50 Spanish EDs. In this group, we identified 99 ACS (incidence: 1.55%, 95% confidence interval [CI]: 1.26–1.89), 69 DVT (1.08%, 1.57–1.72), 353 PE (5.53%, 4.97–6.14), 134 strokes (2.11%, 1.77–2.49; 85% ischemic and 15% hemorrhagic) and 73 UGB (1.14%, 0.90–1.44). SARS-CoV-2 infection was demonstrated in 76% of these cases by polymerase chain reaction (PCR) in nasopharyngeal swab, while diagnosis was established based on signs/symptoms of COVID-19 and/or in typical chest X-ray or computerized tomography findings in the remaining 24%, taking into account the epidemiological context of the enormous number of people infected by SARS-CoV-2 and the shortage of PCR tests experienced worldwide in March–April 2020. The control group included 1,125,491 non-COVID patients (pre-COVID period: 782,125; COVID period: 343,366), with 2701 ACS (3.55%, 3.44–3.66), 1,147 DVT (1.64%, 1.57–1.72), 766 PE (1.23%, 1.16–1.0.29), 2995 strokes (4.43%, 4.31–4.55; 86% ischemic, 14% hemorrhagic) and 1,371 UGB (1.94%, 1.86–2.03). There were few differences in the age demographic data and comorbidities of cases and controls presenting cardiovascular/hemostatic manifestations (Table 1). Remarkably, COVID patients with

UGB and ACS were older than non-COVID patients, and those with PE were younger. Additionally, COVID patients with PE were less frequently women and less frequently had active cancer.

According to relative frequencies, PE was more frequent in COVID than in non-COVID patients in the ED (odds ratio: 4.53, 95% CI: 4.03–5.10), while ACS, DVT, stroke and UGB were significantly less frequent (0.44, 0.36–0.53; 0.66, 0.52–0.84; 0.47, 0.40–0.56; and 0.59, 0.47–0.74; respectively). Similar results were found comparing COVID patients with non-COVID patients recruited during the pre-COVID and the COVID periods separately (Fig. 1). When comparing the relative frequencies of the five cardiovascular/hemostatic manifestations in EDs comers of 2020 with those of 2019, PE was markedly and significantly increased (OR = 2.13, 95%CI= 1.95–2.32), and DVT, stroke and UGB showed less marked, albeit also statistically significant, increments (OR= 1.33, 95%CI= 1.27–1.40; OR= 1.27, 95%CI= 1.17–1.0.39; and OR= 1.26, 95%CI= 1.17–1.0.37; respectively). The relative frequency of ACS was practically identical in 2020 and 2019.

## 4. Discussion

We quantified the frequency of five cardiovascular/hemostatic manifestations in COVID patients at ED consultation before hospitalization. We acknowledge these relative frequencies do not correspond to the real relative frequency of these entities in the general population as they were obtained in ED comers. On one hand, it should be highlighted that only about 10% of COVID patients consulted the ED during the pandemic in Spain; therefore, incidences could be up to 10 times lower. Nonetheless, it is expected that most of the patients presenting the cardiovascular/hemostatic entities analyzed finally attended an ED for health care. The exception to this assumption is that during the 2020 lockdown patients with mild manifestations might have remained at home [10–12]. On the other hand, manifestations developed during hospitalization were not taken into account, and their inclusion would have led to an (unknown) increase of our estimates. However, these episodes could result from hospitalization complications rather than directly to the pathogenesis of SARS-CoV-19, and additionally, from the selection of the sickest patients who are usually hospitalized. For example, while this study showed a relative PE frequency of 0.5% (353/63,822) in COVID patients, single center case-series reported a relative PE frequency of 2.6% (10/388) [4] and 8.2% (23/280) in hospitalized patients, and 20.6% (22/107) [6] in patients admitted to intensive care. Remarkably, using the same comparator (non-COVID patients in the ED, altogether or separated by pre-COVID and COVID period ED comers), PE was increased more than 4 fold while the remaining cardiovascular/hemostatic processes decreased by about half. This suggests that PE is probably a highly frequent entity during SARS-CoV-2 infection, being greater than expected in ED populations and also having the highest increased risk among cardiovascular/hemostatic processes.

Our finding of an increased relative frequency of PE during 2020 with respect to 2019 suggests that part of this increase was due to the COVID pandemic. Conversely, the statistically significant increases of UGB, stroke and DVT in 2020 were lower, and the role of SARS-CoV-2 in these increments would not be as clear as in PE. In fact, PE was one of the first systemic complications that clinicians noted in COVID patients [3,6,13], and it is currently a matter of intense research. It has been suggested that some PE in COVID patients could develop in situ in lungs, favored by a highly inflammatory involvement in a pathophysiological process known as “immunothrombosis” [14–16]. In this sense, alveolar injury and the inflammatory storm present during COVID-19 pneumonia along with disruption of the thrombo-protective state of the pulmonary vascular endothelial cells might contribute to the formation of deep small vessel thrombi in the absence of other classical risk factors such as estrogenic treatment, immobilization or cancer. Our finding of a lower increase in DVT than in PE in COVID patients, as well as the significantly lower frequency of women and cancer in PE

**Table 1**

Comparison between cases and controls that developed one of the five cardiovascular/hemostatic entities analyzed in the UMC-19-S<sub>2</sub> study. Comparisons were made in 73 pairs of COVID and non-COVID patients with upper gastrointestinal bleeding, 134 pairs with stroke, 353 pairs with pulmonary embolism, 69 pairs with deep venous thrombosis, and 99 pairs with acute coronary syndrome.

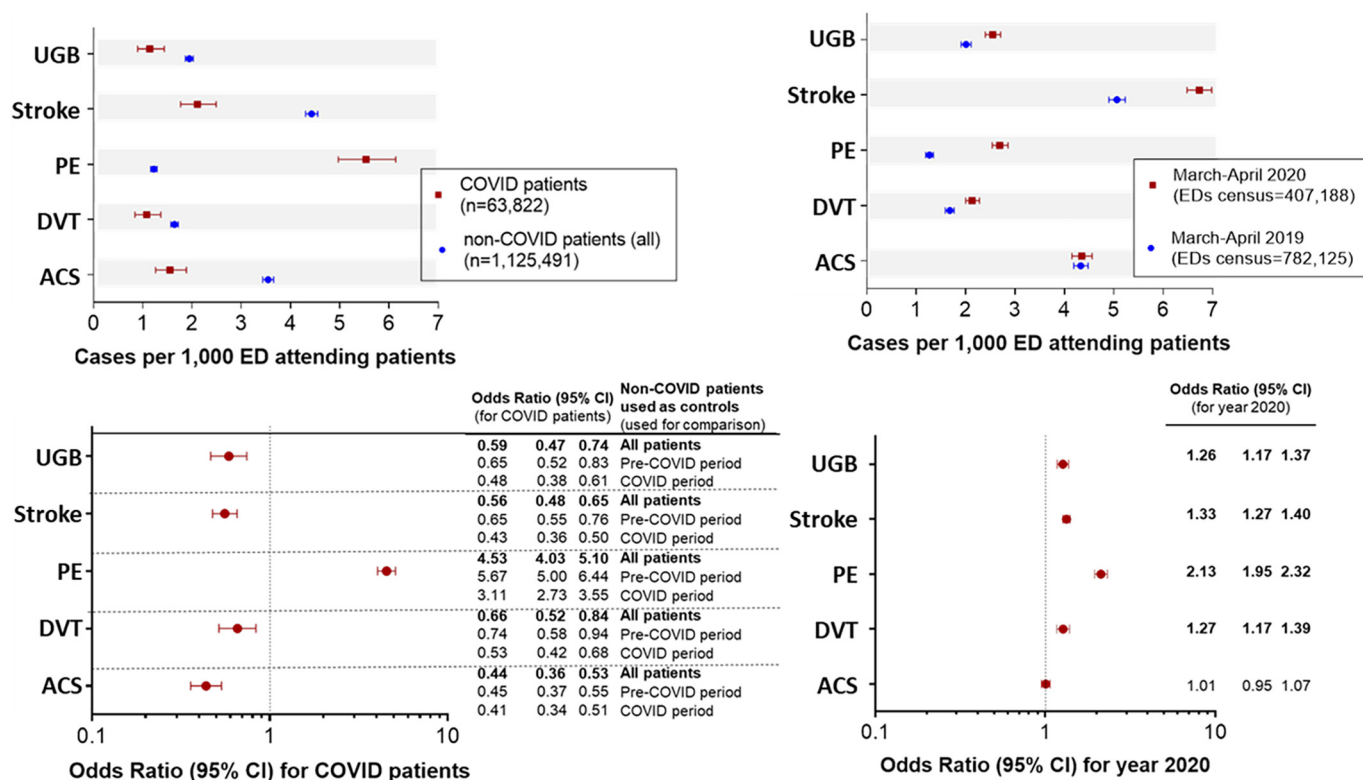
	Upper gastrointestinal bleeding (COVID/non-COVID)	Stroke (COVID/non-COVID)	Pulmonary embolism (COVID/non-COVID)	Deep venous thrombosis (COVID/non-COVID)	Acute coronary syndrome (COVID/non-COVID)
Age [mean (SD)]	77 (15) vs 70 (17) <i>P</i> = 0.020	74 (13) vs 76 (12) <i>P</i> = 0.215	<b>65 (16) vs 68 (17)</b> <i>P</i> = <b>0.026</b>	69 (15) vs 65 (19) <i>P</i> = 0.170	<b>75 (13) vs 66 (14)</b> <i>P</i> < <b>0.001</b>
Female	38% vs 41% <i>P</i> = 0.735	49% vs 40% <i>P</i> = 0.179	<b>42% vs 53%</b> <i>P</i> = <b>0.007</b>	44% vs 51% <i>P</i> = 0.394	31% vs 32% <i>P</i> = 0.879
Hypertension	66% vs 62% <i>P</i> = 0.606	65% vs 75% <i>P</i> = 0.084	47% vs 52% <i>P</i> = 0.287	58% vs 46% <i>P</i> = 0.173	81% vs 65% <i>P</i> = 0.011
Dyslipidemia	43% vs 38% <i>P</i> = 0.613	46% vs 53% <i>P</i> = 0.272	39% vs 36% <i>P</i> = 0.971	29% vs 28% <i>P</i> = 0.850	58% vs 50% <i>P</i> = 0.254
Diabetes mellitus	32% vs 23% <i>P</i> = 0.266	29% vs 31% <i>P</i> = 0.789	18% vs 16% <i>P</i> = 0.535	13% vs 10% <i>P</i> = 0.595	32% vs 28% <i>P</i> = 0.536
Obesity (clinically estimated)	15% vs 22% <i>P</i> = 0.286	13% vs 17% <i>P</i> = 0.396	15% vs 18% <i>P</i> = 0.267	23% vs 19% <i>P</i> = 0.531	18% vs 21% <i>P</i> = 0.592
Coronary artery disease	14% vs 7% <i>P</i> = 0.173	18% vs 13% <i>P</i> = 0.313	6% vs 5% <i>P</i> = 0.589	4% vs 3% <i>P</i> = 0.649	47% vs 38% <i>P</i> = 0.250
Chronic heart failure	11% vs 15% <i>P</i> = 0.461	10% vs 11% <i>P</i> = 0.690	3% vs 5% <i>P</i> = 0.118	1% vs 9% <i>P</i> = 0.052	16% vs 8% <i>P</i> = 0.082
Chronic obstructive pulmonary disease	15% vs 8% <i>P</i> = 0.197	10% vs 12% <i>P</i> = 0.555	7% vs 11% <i>P</i> = 0.058	4% vs 12% <i>P</i> = 0.116	14% vs 14% <i>P</i> = 1,000
Active cancer	19% vs 15% <i>P</i> = 0.372	13% vs 19% <i>P</i> = 0.187	<b>13% vs 26%</b> <i>P</i> < <b>0.001</b>	15% vs 16% <i>P</i> = 0.813	12% vs 14% <i>P</i> = 0.674
Dementia	18% vs 10% <i>P</i> = 0.149	13% vs 9% <i>P</i> = 0.245	7% vs 9% <i>P</i> = 0.325	7% vs 7% <i>P</i> = 1.000	9% vs 6% <i>P</i> = 0.420

Bold numbers denote comparisons being statistically significant (*p* < 0.05).

in COVID patients respect to PE in non-COVID patients would suggest such hypothesis.

Some limitations impose caution in interpreting our findings. In many cases the diagnosis was based on clinical/radiological findings, with no

microbiological confirmation, although this was the rule in Spanish (and many countries) EDs due to test shortage [17,18]. During the COVID-19 pandemic, emergency physicians have had a lower threshold for ordering some diagnostic studies (computerized tomography



**Fig. 1.** Comparison of frequency of the five cardiovascular/hemostatic entities assessed in the UMC-19-S<sub>2</sub> study in COVID-19 and non-COVID patients attending emergency departments (upper panel) and odds ratios for COVID with respect to non-COVID patients (lower panel; graph on the left represents only odds ratios obtained from comparison with all non-COVID control patients, while odds ratios obtained from separate comparison with non-COVID patients coming from the pre-COVID and the COVID periods are presented in the table at the right). UGB: upper gastrointestinal bleeding; PE: pulmonary embolism; DVT: deep venous thrombosis; ACS: acute coronary syndrome.



pulmonary angiograms, Doppler ultrasonography), and the number of diagnosis could actually have been higher. Patient-related or disease-related factors could, to some extent, have accounted for decreased/increased relative frequencies, and we did not adjust for them. Finally, ED patients and disease typology could have differed during the COVID outbreak (due to country lockdown), although the similar rates observed for COVID patients for the five cardiovascular/hemostatic manifestations using both subgroups of controls (from the pre-COVID and the COVID periods) do not support this possibility. In addition, by comparing rates between 2020 and 2019, the relative frequency of PE among ED comers remained overtly increased.

Despite all these limitations, the UMC-19-S<sub>2</sub> study shows that PE was clearly increased in ED comers during the 2020 period, suggesting that this increase may be linked to SARS-CoV-2 infection. The role of SARS-CoV-2 in the mild increments observed in DVT, stroke and UGB needs to be further investigated.

## Authors contribution

All authors discussed the idea and design of study and provided patients. Data analysis and first draft writing was done by OM. All authors read such a draft and provided insight for the final version. OM is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

## Declaration of Competing Interest

None author reported any conflict of interest directly or indirectly connected with this manuscript.

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